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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/735,203
Filing Date: December 12, 2003
Appellant(s): COSENZA, LAWRENCE W.

Avery N. Goldstein, Ph.D.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/24/09 appealing from the Office action mailed 8/24/07.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is deficient. 37 CFR 41.37(c)(1)(v) requires the summary of claimed subject matter to include: (1) a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number, and to the drawing, if any, by reference characters and (2) for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function as

permitted by 35 U.S.C. 112, sixth paragraph, must be identified and the structure, material, or acts described in the specification as corresponding to each claimed function must be set forth with reference to the specification by page and line number, and to the drawing, if any, by reference characters. The brief is deficient because the summary of claimed subject matter neglects to indicate that examination of the claimed subject matter has been limited to a single invention of a sacromastigophoric organism comprising a "drug or prodrug" as the therapeutic agent packaged within, and a single species of "Trypanosome" as the sacromastigophoric organism. A restriction requirement and an election of species requirement was mailed to appellant on 9/8/06. The appellant responded on 9/21/06 and elected **without traverse** the invention of Group VII, a therapeutic delivery system comprising a drug or prodrug, for examination, the species of "Trypanosome" as the sacromastigophoric agent. While claim 2 is limited to "drug or prodrug" as the therapeutic agent, and claim 11 is limited to a trypanosome, none of the claims are limited to both the elected invention and elected species. Thus, the claimed subject matter of claims 1-2, 4, 7-8, 11 and 41 has only been examined to the extent that it reads on the elected invention of a drug or prodrug as the therapeutic agent and the species of "Trypanosome" as the sacromastigophoric organism, as neither the linking claim nor the generic claims are allowable.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows: although not clearly set forth in the advisory action mailed on 2/29/08, the rejections of claims 7, 11, and 41, and all claims dependent

therefrom, under 35 U.S.C. 112, second paragraph, for indefiniteness were withdrawn in view of the after-final amendment to the claims submitted by appellant on 12/21/07 and entered by the examiner on 2/29/08. Therefore, no claims are rejected under 35 U.S.C. 112, second paragraph.

The grounds of rejection to be reviewed on appeal are limited to two rejections, the rejection of claims 1-2, 4, 7-8, 11, and 41 under 35 U.S.C. 112, first paragraph for insufficient written description, and the rejection of claims 1-2, 4, 7-8, 11, and 41 under 35 U.S.C. 112, first paragraph, for lack of enablement.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Smith et al. (1995) Science, Vol. 268, 284-286

Shimamura et al. (2001) Mol. Biochem. Parasitol., Vol. 115,227-237

U.S. Patent 4,356,167

U.S. Patent 4,873,088

U.S. Patent 5,843,475

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1) Claims 1-2, 4, 7-8, 11, and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide sufficient written description for the genus of genes encoding primate Hpr proteins other than a cDNA encoding human Hpr. The specification discloses that a factor found in human serum known as haptoglobin-related protein (Hpr) can induce lysis of *Trypanosoma brucei*. The specification further provides guidance for cloning the nucleic acid encoding human Hpr from the human hepatic carcinoma cell line HepG2. However, aside from the human Hpr cDNA sequence and encoded amino acid sequence, the specification does not provide any additional description for any other Hpr genes or proteins from any other primate species. The genus of primate is large, comprising more than 200 species. However, at the time of filing, circa 2002, the prior art did not teach a single functional non-human primate Hpr gene. Smith et al. teaches that serum lytic activity is only observed in some apes and Old World monkeys, not in other non-primate species, and that in non-human primates the only known Hpr gene is found in Chimpanzees, where the gene does not express functional protein due to premature termination of translation (Smith et al. (1995) Science, Vol. 268, 284-286, see pages 285-286, bridging paragraph). Smith et al. establishes that at the time of filing, the prior art did not teach a single full length non-human Hpr gene from any primate species, and that the Chimpanzee gene reported in the prior art was a pseudogene incapable of expressing functional protein. Further, neither the specification nor the prior art teaches, suggests, or exemplifies the

level of sequence and/or structural homology or shared common structure(s) between primate Hpr genes, or teaches which non-human primate species actually possess a functional Hpr gene versus a non-functional pseudogene.

The Revised Interim Guidelines state, " when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus .....In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, of the Revised Interim Guidelines for Written Description). The instant claims are in fact analogous to Example 15 of the Written Description Training Materials published on March 25, 2008. This example provides an analysis of written description for a claim to a genus of nucleic acids encoding a mammalian protein where only a single species, the mouse gene, was disclosed. In the analysis, it was pointed out that disclosure of the nucleic acid sequence of a single species, where no common structural feature had been established between members of the genus, was inadequate to establish written description of the genus. In the instant case, an additional level of complexity exists as the prior art taught that the only other known primate Hpr sequence, the chimpanzee sequence, was a pseudogene sequence rather than a functional Hpr gene sequence.

It is further noted that *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented

what is claimed." (See Vas-Cath at page 1116). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the appellant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). The appellant has not provided any description or reduction to practice of any primate Hpr nucleic acid other than human Hpr. Based on the appellant's specification and the state of the art for Hpr gene sequences at the time of filing, the skilled artisan cannot envision the detailed chemical structure of the genus of primate Hpr genes encompassed by the claims. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Thus, for the reasons outlined above, the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph.

2) Claims 1-2, 4, 7-8, 11, and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims on appeal have been the subject of both a restriction requirement and an election of species requirements. As noted above, a restriction requirement and an election of species requirement was mailed to appellant on 9/8/06. The appellant responded on 9/21/06 and elected **without traverse** the invention of Group VII, a therapeutic delivery system comprising a drug or prodrug, for examination, the species of "Trypanosome" as the sacromastigophoric agent. While claim 2 is limited to "drug or prodrug" as the therapeutic agent, and claim 11 is limited to a trypanosome, none of the claims are limited to both the elected invention and elected species. Thus, the claimed subject matter of claims 1-2, 4, 7-8, 11 and 41 has only been examined to the extent that it reads on the elected invention of a drug or prodrug as the therapeutic agent and the species of "Trypanosome" as the sacromastigophoric organism, as neither the linking claim nor the generic claims are allowable.

There are three specific issues of enablement: 1) the specification does not provide an enabling disclosure for making and using a Trypanosome containing a gene or cDNA encoding a non-human primate Hpr, 2) the specification does not provide an enabling disclosure for delivering a drug or prodrug by lysing any species of Trypanosome containing the drug through expression of human Hpr, and 3), the specification does not provide an enabling disclosure for packaging a drug or prodrug in a trypanosome as claimed for use as a drug delivery system.

Regarding issue 1), the specification discloses making a Trypanosome containing an expression construct comprising a gene for a primate Hpr, and specifically a full-length primate Hpr, for use as a therapeutic delivery system for drugs such that administration of the Trypanosome containing the drug and expression construct results in drug delivery to the host following lysis of the Trypanosome by the expressed lytic factor, Hpr. As discussed above in the rejection of the claims for lack of written description, the specification does not provide sufficient guidance for any gene or nucleic acid encoding a primate Hpr other than a cDNA encoding human Hpr. The specification further fails to provide guidance concerning any common structural features shared between members of the genus of primate Hpr genes or the level of sequence homology between the species. The genus of primate is large, comprising more than 200 species. However, at the time of filing, circa 2002, the prior art did not teach a single functional primate Hpr gene other than human Hpr. Smith et al. teaches that serum lytic activity is only observed in some apes and Old World monkeys, not in other non-primate species, and that in non-human primates the only known Hpr gene is found in Chimpanzees, where the gene does not express functional protein due to premature termination of translation (Smith et al. (1995) Science, Vol. 268, 284-286, see pages 285-286, bridging paragraph). Smith et al. establishes that at the time of filing, the prior art did not teach a single full length non-human Hpr gene from any primate species, and that the Chimpanzee gene reported in the prior art was a pseudogene incapable of expressing functional protein. As such, the prior art establishes the unpredictability in knowing *a priori* whether any additional functional Hpr gene sequences were present in any of the approximately 200 primate species other than human. As such, due to the state of the art of non-human primate Hpr genes at the time of filing which teaches a single non-

functional chimpanzee pseudogene, the lack of guidance provided by the specification for species of primate Hpr genes other than human, and the breadth of the claims, it would have required undue experimentation to isolate and use any primate species of Hpr gene other than human Hpr in the claimed trypanosome.

Regarding issue 2), the specification further fails to provide sufficient guidance for lysing any species of Trypanosome through expression of human Hpr. The claims are drawn to a "therapeutic delivery system". As noted above, the specification discloses that drugs can be delivered using a Trypanosome as claimed through the action of the Hpr gene product which induces lysis of the Trypanosome in a host cell thereby releasing the therapeutic drug present in the Trypanosome. The specification broadly discloses making and using any Trypanosome species for drug delivery. The specification further discloses the construction of an inducible expression construct comprising the cDNA for human Hpr operatively linked to a p67 lysosomal targeting sequence and further operatively linked to an tetracycline inducible T7 promoter, as shown in Figure 9. While the working examples teach the construction of an expression vector as shown in Figure 9 and described above, the examples do not include any data from any actual experiments demonstrating any species of Trypanosome modified to contain this expression vector, or the inducible lysis of the modified Trypanosome mediated by expressed human Hpr. Please note that examples 5 and 6 in the specification appear to be prophetic examples describing experiments to test the ability of Trypanosomes containing an expression vector to mediate gene transfer of a provirus in human or mice cells *in vitro* or *in vivo*. These prophetic examples do not demonstrate actual lysis of Trypanosomes in infected cells through expression of Hpr. Further, the prior art is clear that human Hpr is not active as a lytic agent against all species of

Trypanosome, not even all species of *Trypanosoma brucei*. Shimamura et al., for instance, clearly teaches that *Trypanosoma brucei rhodensiense* is not lysed by Hpr or the TLF complex comprising Hpr (Shimamura et al. (2001) *supra*, page 227). The specification does not provide any specific guidance for using Hpr to lyse any species of Trypanosomes other than *Trypanosoma brucei brucei*, and further does not provide any actual working examples demonstrating lysis of any Trypanosome including *Trypanosoma brucei brucei* through the expression of Hpr from a recombinant construct. It is also noted that the specification on page 3, which discloses several species and subspecies of Trypanosomes including the *T. brucei* subspecies *rhodesiense, gambiense, and brucei*, states in regards to the subspecies *T. brucei brucei* that "[t]his organism is morphologically and biochemically similar to the other two *T. brucei* subspecies **but** is sensitive to a non-immune factor in human serum called haptoglobin-related protein (Hpr)" (specification, page 3, emphasis added by the examiner). Thus, the specification, through the use of the word "but", appears to indicate that sensitivity to Hpr is not shared by the other *T. brucei* subspecies. It is also noted that the specification clearly teaches that the lysis of the Trypanosome is required to release the therapeutic agent such that inability of Hpr to lyse the majority of subspecies of *Trypanosoma brucei* would prevent the use of such Trypanosomes as drug delivery vehicles. Therefore, in view of the state of the art of Hpr and Hpr lytic activity of Trypanosomes, the limited guidance provided by the specification for lysing any Trypanosome including all subspecies of *Trypanosoma brucei,* and the breadth of the claims, it would have required undue experimentation to make and use any species of Trypanosome, including the subgenus of *Trypanosoma brucei,* as a drug delivery system.

Regarding issue 3), the specification further fails to provide sufficient guidance for packaging a therapeutic drug or prodrug in a trypanosome or for delivering any drug or prodrug to any host cell using the modified Trypanosomes as claimed. As noted above, the working examples, both actual and prophetic, are drawn to the delivery of a provirus, not a drug or prodrug. The only guidance relevant to drug delivery provided by the specification occurs on page 18, which states that, "Non-nucleic acid therapeutic agents are packaged in a sacromastigophoric organism through electroporation or phagocytosis of liposomally packaged therapeutic agents" (specification, page 18, lines 8-10). It is noted, however, that the claims are not limited to Trypanosomes containing liposomally packaged drugs or prodrugs. The specification then points to US Patents 4,356,167, 4,873,088, and 5,843,475 as providing guidance for liposomal packaging processes or electroporation. However, these patents, while teaching methods to make liposomes containing various chemical compounds or drugs, do not provide any guidance for actually introducing the liposomes into a Trypanosome or further teach the fate of such liposomes once in the Trypanosome, nor do they teach the electroporation of a Trypanosome for the introduction of a drug. Neither the specification nor the prior art teach that drugs, either packaged in a liposome as described by any of the reference patents or not, can be introduced and stably maintained in a Trypanosome, or subsequently released to a host organism upon lysis of the Trypanosome. Further, while the specification on page 18 goes on to teach that the organism containing a non-nucleic acid therapeutic must be administered in a therapeutic amount, the specification fails to teach how much of any type of drug can be contained within a single Trypanosome or what amount of drug containing Trypanosome must be delivered to

release a therapeutic amount of the drug to a host. The appellant is reminded that the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.
> *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1005 (CAFC 1997). (emphasis added).

Thus, in view of the state of the art, which does not teach the inclusion of drugs or prodrugs in Trypanosomes or the use of such Trypanosomes to deliver therapeutic amounts of drugs to a host, the lack of any specific guidance for modifying a Trypanosome to contain any amount of any drug or prodrug, the lack of working examples, and the breadth of the claims, it would have required undue experimentation to make and use the Trypanosomes as claimed.

(10) Response to Argument

1) The rejection of claims 1-2, 4, 7-8, 11, and 41 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, has been traversed by the appellant. Appellant's arguments have been fully considered but have not been found persuasive in overcoming the rejection of record.

The appellant initially sets forth requirements for satisfying written description, supported by case law citations. There is no dispute over these requirements. However, the position of the Office is that the appellant has not met these requirements for the claimed invention.

The appellant argues that the disclosure of SEQ ID NO:28, the cDNA for full length human Hpr, in the specification provides sufficient written description for the genus of primate Hpr. The appellant argues that it is known by one of skill in the art that Hpr genes are only found in humans, gorillas, mandrills, chimpanzees, and sooty mangabeys. The appellant then states that of these only humans, baboons, and chimpanzees possess full length Hpr and that these genes exhibit high sequence homology. Therefore, according to appellant, the total number of primate Hpr is three, and that in view of the sequence homology and the size of the genus, the disclosure of a single species, human Hpr, is sufficient to demonstrate possession of the genus.

In response, the appellant has not cited any evidence supporting their statements that the skilled artisan at the time of filing knew of the existence of full length Hpr genes from baboons and chimpanzees, let alone of non-full length and/or pseudogene Hpr sequences in gorillas, mandrills, chimpanzees, and sooty mangabeys. It is noted this argument has been made by appellant previously, see the responses filed on 3/6/07 and 12/21/07, and that while the appellant previously cited a post-filing article published in 2004 in support of their position, this article was never provided or made of record for examiner's consideration. Concerning knowledge acquired years after filing, it is noted that compliance with 35 U.S.C. 112, first paragraph, for written description is determined based on the disclosure in the specification in view of the state of the art at the time of filing. See MPEP 706.03. See also form paragraph 7.31.01 which states;

"[t]he claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (emphasis added by examiner). The rejection of record discussed the disclosure in the specification in view of the state of the prior art and concluded that the specification does not provide sufficient written description for the genus of primate Hpr genes other than a human Hpr cDNA. The rejection of record also pointed out that aside from the human Hpr nucleic acid sequence and encoded amino acid sequence, the specification does not provide any additional description for any other Hpr genes or proteins from any other species of animal including the genus of primates or provide any information concerning sequence or structural similarities between different species of primate Hpr genes. Further, the rejection of record cited Smith et al., which was published prior to the filing date of the instant application and which represents the extent of what was known concerning non-human primate Hpr and Hpr genes prior to the time of filing. Smith et al. teaches that serum lytic activity, which may or may not be due to the activity of Hpr, is only observed in some apes and Old World monkeys, not in other non-primate species, and that in non-human primates the only known Hpr gene is found in Chimpanzees, where the gene does not express functional protein due to premature termination of translation (Smith et al. (1995) Science, Vol. 268, 284-286, see pages 285-286, bridging paragraph). Appellant concedes on page 9 of the Appeal Brief that Smith et al. teaches that the chimpanzee gene is a non-functional pseudogene but suggests that now the skilled artisan is aware of a full length chimpanzee Hpr gene. However, such an unsubstantiated statement does not establish what the skilled artisan knew at the time of filing. The evidence of record does not support appellant's claim that only three

species of primate Hpr exist, that the sequences share substantial homology, or that the skilled artisan was aware of any of these three species of primate Hpr genes other than the human Hpr gene at the time of filing. Thus, neither the specification nor the prior art provides an adequate description for any Hpr gene or protein other than human Hpr. Therefore, while appellant argues that that there are three species of primates that express the full length Hpr gene, this does not reflect the knowledge of the skilled artisan at the time of filing and does not show that the appellant was in possession of the genus of primate Hpr as of 2002 , the effective filing date.

The appellant further argues that the absence of scientific findings in the prior art for additional species of primate genes is indicative of the size of the genus of primate Hpr and that the recitation of the term Hpr is alone sufficient to describe the genus of primate Hpr genes similar to the use of the generic term halogen found to be sufficient for written description for the genus of halogens in *Bigham v. Godtfredsen*. In response, it is first noted that there is no analogy between the genus of halogens, which is an extremely well known and established group of elements, and a genus of primate Hpr genes of which even the size of the genus was unknown at the time of filing. As discussed above, only a single functional primate Hpr gene, the human gene, had been cloned as of the effective filing date of the instant invention. A second gene, in Chimpanzees, was taught in the prior art to be a non-functional pseudogene. With more than 200 species of primates and the prior art recognized potential for pseudogenes, the size of the genus was clearly not known in the prior art and was not described in the specification. Further, the lack of publications regarding additional primate Hpr genes does not establish or suggest a small size for the genus since the lack of teachings in the prior art is not evidence that the skilled artisan looked for other primate Hpr genes and that no additional genes were found. There is

simply no way of knowing without the benefit of hindsight why the prior art does not teach additional primate species, i.e. there is no way to know whether a search for additional species had been made or not prior to the effective filing date. Thus, the Office strongly disagrees that one of ordinary skill in the art would have been aware of ultimate size of the genus of primate Hpr genes at the time of filing in 2002.

Finally, appellants argument that a written description need not, and should not, disclose all "art-recognized equivalents", citing *Vas-Cath Inc. v. Mahurkar*, is not compelling since there is no evidence of record that any "art-recognized equivalent" to the human Hpr gene was in fact known in the prior art. Therefore, it is maintained that the specification fails to adequately describe the genus of claimed primate Hpr genes as required by 35 U.S.C. 112, first paragraph.

2) The rejection of claims 1-2, 4, 7-8, 11, and 41 under 35 U.S.C. 112, first paragraph, for lack of enablement, has been traversed by the appellant. Appellant's arguments have been fully considered but have not been found persuasive in overcoming the rejection of record.

It is first noted that on page 16, paragraph 2, the appellant provides an argument for an issue of enablement that is not part of the rejection under Appeal. The appellant argues that since the Hpr gene is under control of a inducible promoter, one could make a Trypanosome as claimed since expression is not constitutive. In response, please note that the issue of constitutive expression was overcome through the appellant's claim amendment filed on 6/6/07 and that this issue was not maintained in the final rejection mailed to appellants on 8/24/07.

The appellant initially sets forth the standard for establishing enablement and for finding that "undue experimentation" is required to make and use a claimed invention, supported by case

law citations. There is no dispute over these requirements. However, the position of the Office is that the appellant has not met these requirements for the claimed invention.

The Office as represented by the examiner of record analyzed the specification in direct accordance to the factors outlined in *In re Wands* and *In re Forman*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of the skilled artisan, and 8) the breadth of the claims, and presented detailed scientific reasons supported by citations from prior art publications for the finding of a lack of enablement for invention as claimed. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). 35 U.S.C. 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Regarding issue 1), the lack of enablement for the genus of primate Hpr genes as set forth in the grounds of rejection section above, the appellant reiterates their remarks made in reference to the genus of primate Hpr genes in response to the written description rejection. Specifically, the appellant argues that the genus of primate Hpr genes is exceedingly small, comprising only three species which possess of high degree of sequence similarity, and that as gene sequencing

techniques were well known at the time of filing, it would not have required undue experimentation to make and use a gene or cDNA encoding any primate Hpr using the human Hpr gene as a starting point.

In response, and as noted above, the appellant has not cited any evidence supporting their statements that the skilled artisan at the time of filing knew that the genus of primate Hpr genes only consisted of three species, or that the skilled artisan at the time of filing knew of the existence of full length Hpr genes from baboons and chimpanzees, let alone of non-full length and/or pseudogene Hpr sequences in gorillas, mandrills, chimpanzees, and sooty mangabeys, There is likewise no evidence present in either the specification or the prior art concerning the level of sequence similarity between the human Hpr gene and any other Hpr gene. However, as set forth in the grounds of rejection, the prior art, as represented by Smith et al., does teach that at the time of filing serum lytic activity, which may or may not be due to the activity of Hpr, is only observed in some apes and Old World monkeys, not in other non-primate species, and that in non-human primates the only known Hpr gene is found in Chimpanzees, where the gene is a pseudogene and does not express functional protein due to premature termination of translation (Smith et al. (1995) Science, Vol. 268, 284-286, see pages 285-286, bridging paragraph). Therefore, while appellant argues that that there are three species of primates with high sequence homology that express the full length Hpr gene, this does not reflect the knowledge of the skilled artisan at the time of filing in 2002 , the effective filing date. Furthermore, Smith et al. teaches that the haptoglobin gene is the product of a gene triplication event that occurred in apes and Old World monkeys early in primate evolution resulting in haptoglobin, the haptoglobin related protein, and the primate haptoglobin gene (Smith et al., pages 265-266, bridging sentence).

However, more importantly, Smith et al. teaches that in humans, a subsequent unequal cross-over resulted a human haptoglobin-related gene which is a hybrid of the haptoglobin-related gene and primate haptoglobin (Smith et al., page 266). Thus, Smith et al. establishes that at the time of filing, the human haptoglobin related protein (Hpr) gene was the product of a special event in humans such that the skilled artisan would not have been able to predict what level of sequence homology might exist between the human gene and any other full-length primate Hpr gene that may exist in another species of primate. Further, because of the apparent special characteristics of the human Hpr gene, it would have required undue experimentation to isolate other potential full-length primate Hpr genes which are not pseudogenes.

Therefore, it is maintained that the analysis of the all the Wands factors, as set forth in the rejection of record and discussed in detail above, does not support a finding of enablement for the invention as claimed in regards to a genus of primate Hpr genes.

Regarding issue 2) the lack of enablement for delivery a drug or prodrug by lysing any species of Trypanosome containing the drug through expression of human Hpr as set forth in the grounds of rejection section above, the appellant argues that the examiner has misunderstood the teachings of Shimamura et al. and that in their opinion Shimamura et al. unequivocally teach that the reason that *Trypanosoma brucei rhodesiense* is not lysed by human serum Hpr protein is because the this subspecies of Trypanosome does not endocytose Hpr, noting that the art published prior to Shimamura et al. teaches that one of the mechanisms of resistance of sleeping sickness trypanosomes (*Trypanosoma brucei rhodesiense*) to human serum is decreased internalization of receptor bound TLF. The appellant further argues that the claimed invention circumvents endocytosis of Hpr by intracellular expression of Hpr with a lysosomal targeting

sequence such that the invention as claimed is fully enabled. The appellant also points to the working examples present in the specification which in appellant's opinion fully enable the invention as claimed.

In response, appellant's interpretation of the teachings of Shimamura et al. is not agreed. While Shimamura et al. suggests that the lack of lysis of *Trypanosoma brucei rhodensiense* may be due to reduced endocytosis and failure to enter the lysosome, Shimamura et al. does not in fact teach that the exact reason for the failure of TLF-1 containing Hpr to lyse *Trypanosoma brucei rhodensiense* had been determined. Shimamura et al. demonstrates that at the time of filing, the activity, and mechanism of activity, of human Hpr was just beginning to be explored. Further, neither Shimamura et al. nor the instant specification demonstrates that improving intracellular targeting of Hpr alone to the lysosome would in fact result in lysis of *Trypanosoma brucei rhodensiense*.

As for the working examples, the rejection of record presented a detailed analysis of the working examples. Although not required, as pointed out by appellant, the presence of working examples is one of the Wands factors that contributes to the analysis of enablement. The working examples in the specification disclose the construction of an inducible expression construct comprising the cDNA for human Hpr operatively linked to a p67 lysosomal targeting sequence and further operatively linked to an tetracycline inducible T7 promoter, as shown in Figure 9. While the working examples teach the construction of an expression vector as shown in Figure 9 and described above, the examples do not include any data from any actual experiments demonstrating the modification of any species of Trypanosome to contain this expression vector, or the inducible lysis of the modified Trypanosome mediated by expressed human Hpr.

Examples 5 and 6 in the specification are prophetic examples describing experiments designed to test the ability of Trypanosomes containing an expression vector to mediate gene transfer of a provirus in human or mice cells *in vitro* or *in vivo*. These prophetic examples do not demonstrate the making of a Trypanosome continuing an expression vector or actual lysis of Trypanosomes in infected cells through expression of Hpr. While the appellant argues that prophetic examples are allowed, this is not the issue. The issue is whether the skilled artisan, familiar with the teachings of Shimamura et al. and the nascent state of the art of Hpr activity at the time of filing, would have predicted that directing expression of human Hpr to the lysosome in any Trypanosome species would in fact result in lysis of the Trypanosome. Appellant's working examples, since they do not actually present any data for any species of Trypanosome containing the expression vector disclosed in Example 1 and Figure 9, or any data regarding the ability of human Hpr to lyse any species of Trypanosome either inside or outside or a host cell, do not overcome the lack of predictability present in the prior art for using the human Hpr protein to lyse any species of Trypanosome by targeting the Hpr protein to the lysosome in a Trypanosome. Therefore, appellant's arguments are not found persuasive in overcoming the rejection of record.

Regarding issue 3), the lack of enablement for packaging a drug or prodrug in a trypanosome as claimed for use as a drug delivery system as set forth in the grounds of rejection section above, the appellant argues that the word "drug" as defined by the specification includes nucleic acid molecules and that Examples 1-3 in the specification teach this embodiment.

In response, the original claim which recited, "a sacromastigophoric organism containing said therapeutic agent" was identified as a linking claim in the restriction requirement which identified several independent and distinct inventions linked by the use of the term "therapeutic

agent". These independent inventions encompassed by "therapeutic agent" included genes, artificial chromosomes, magnetic species, radioactive species, vitamins, nanocrystals, and drugs or prodrugs. In response to this restriction requirement, the appellant elected without traverse the invention drawn to an organism containing a drug or prodrug. While the specification broadly defines a "therapeutic agent" to include various substances capable of treating a disease, it is not agreed that the specification broadly defines a "drug or prodrug" to encompass the same breadth of compounds as encompassed by a "therapeutic agent". Page 11 of the specification provides the definition of drug/prodrug. This entire paragraph is set forth below for clarity:

> The term "drug" is defined as compounds used as a medicine to treat a disease, disease system, or undiagnosed pain. Drugs, as used herein, are typically small organic molecules having a molecular weight of less than 1000 and illustratively include channel blockers, receptor blockers, steroids, opioids, platinum compounds, terpenoids, and alkaloids. As used herein, drugs include pharmaceutically acceptable salts, esters, and amides of active medicinal species.
>
> The term "prodrug" is defined as compounds that are rapidly transformed in vivo to yield the parent compounds of the above formula, for example, by hydrolysis in blood. (T. Higuchi et al. 1987). (emphasis added by the examiner)

Thus, contrary to appellant's arguments, drugs are taught in the specification to be small organic molecules having a molecular weight of less than 1000 and include channel blockers, receptor blockers, steroids, opioids, platinum compounds, perenoids and alkaloids. The rejection of record set forth above in Section 9 of this Examiner's Answer provided a detailed analysis of the Wands factors as to why the as filed specification fails to provide an enabling disclosure for making and using a Trypanosome containing a drug or prodrug through packaging as claimed. The appellant

has not provided in their Appeal Brief any arguments traversing the actual grounds of rejection for this issue. As such, the rejection of record is maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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